

INRAE

ELIANCE
Des éleveurs. Une ambition.

Oniris
ÉCOLE NATIONALE
VÉTÉRINAIRE, AGRICOLE ET DE L'ALIMENTATION



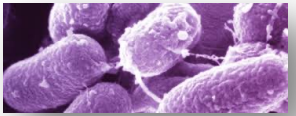
Selection for resistance to paratuberculosis in Holstein cattle

Marie-Pierre Sanchez

marie-pierre.sanchez@inrae.fr

Bovine paratuberculosis or Johne's disease

Endemic, contagious, and incurable disease due to *Mycobacterium avium subsp. paratuberculosis* (MAP)



Early contamination

In utero or during 1st months by contact with feces



Non-clinical cases

Weight loss & reduced milk production



Clinical cases

Chronic diarrhea, rapid weight loss & death



Infected animals without symptoms & non shedders

Infected animals without symptoms & **shedders**

Infected animals **with symptoms** & **strongly shedders**

Bovine paratuberculosis or Johne's disease

Serious economic consequences
& adverse effects on animal welfare

Very difficult to control disease



Gut lesions

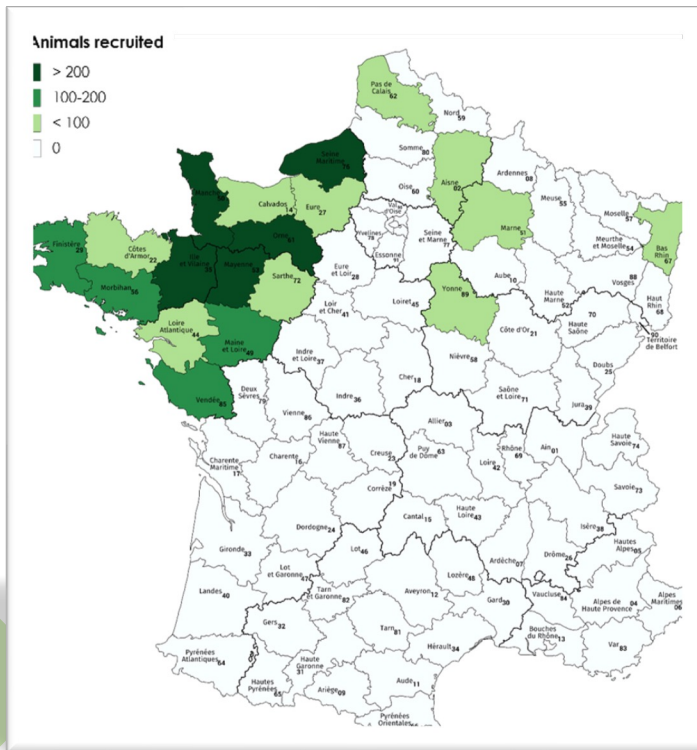


Rapid weight loss

- ☑ Long latency period
- ☑ No effective treatment, restricted vaccine
- ☑ Diagnostic tests (fecal culture, serum/milk ELISA, fecal PCR...) have varying **sensitivities/specificities depending** on the stage of infection => need to repeat testing

A better genetic resistance may help to control the disease

Earlier studies (PICSAR/PARADIGM)



1644 Holstein Cows
with concordant & reliable statuses were genotyped

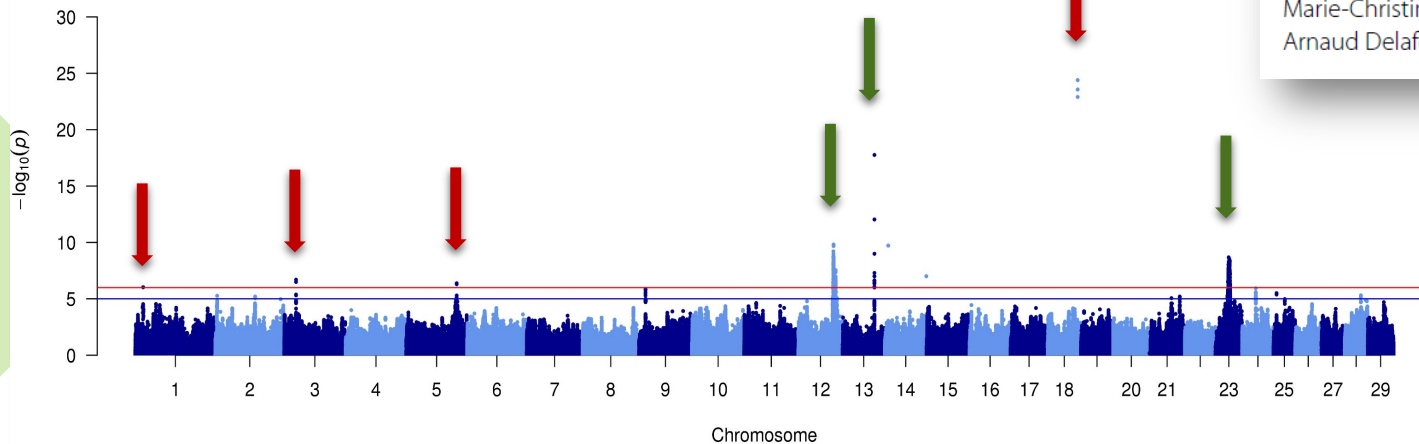
	Holstein
Cases *	806
Controls	838
Total	1644
* incl. clinical cases Clinical symptoms & MAP in feces	229

Earlier studies (PICSAR/PARADIGM)

GWAS from imputed whole genome sequences
From 1000 BG population

- RUN6 published in GSE in 2020
- RUN8 presented at EAAP in 2021

9 QTL on chr. 1, 3, 5,
12, 13, 14, 18 & 23



Best candidate SNPs added on the EuroGMD BeadChip

Sanchez et al. *Genet Sel Evol* (2020) 52:14
<https://doi.org/10.1186/s12711-020-00535-9>

GSE Genetics
Selection
Evolution

RESEARCH ARTICLE

Open Access



Identification of the *ABCC4*, *IER3*,
and *CBFA2T2* candidate genes for resistance
to paratuberculosis from sequence-based GWAS
in Holstein and Normande dairy cattle

Marie-Pierre Sanchez^{1*}, Raphaël Guatteo², Aurore Davergne³, Judikael Saout¹, Cécile Grohs¹,
Marie-Christine Deloche^{1,4}, Sébastien Taussat^{1,4}, Sébastien Fritz^{1,4}, Mekki Boussaha¹, Philippe Blanquefort⁵,
Arnaud Delafosse⁶, Alain Joly⁷, Laurent Schibler⁴, Christine Fourichon² and Didier Boichard¹

First **genomic predictions** after
estimating SNP effects with a Bayesian
approach but the accuracy in a validation
population of Holstein cows was too low
for selection purpose

Towards a Single Step approach

New large dataset in Holstein

~ 250,000 cows with serological statuses (infected / non-infected) incl. a few thousand with genotypes

- Many cows with **statuses but not genotyped**
- Among the cows with statuses, most have **sires** and/or **maternal grand-sires with genotypes**

To consider all this information, we applied a **Single Step** approach that can help in obtaining more accurate genomic predictions

Objectives

By combining all the available data in Holstein in a Single Step GBLUP (ssGBLUP) approach, a two-fold objective :

- 1) To further investigate the **genetic determinism** of resistance to paratuberculosis (h^2 & QTL)
- 2) To estimate **genetic trends, reliability, and risk factors** associated with genomic predictions



Data filtering

247,375 Holstein cows with statuses

Incl. 4100 cows PICSAR/PARADIGM
+ cows with statuses deduced from
serological tests (Idexx & Idvet ELISA)
recorded since 2015

Non-infected

228,337



Infected

19,038



Selection of cows

Exposed to MAP

- controls were at least 3 years old
- herds with at least one infected and one non-infected cow born in the same year

42,829



56,766 Holstein cows
from 3114 herds

13,937



Single Step approach

Pedigree

	Total number of animals	Animals with genotypes
Animals in the pedigree	161,253	12,431
Incl. cows with statuses	56,766	4031

Model

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{a} + \mathbf{e}$$

\mathbf{y} = vector of statuses (1 for controls / 0 for cases)

$\boldsymbol{\beta}$ = vector of fixed effects herd x birth year, birth month, ELISA test

\mathbf{a} = vector of random genetic effects $\mathbf{a} \sim \mathbf{N}(\mathbf{0}, \mathbf{H}\sigma_a^2)$

\mathbf{e} = vector of random residual effects $\mathbf{e} \sim \mathbf{N}(\mathbf{0}, \mathbf{I}\sigma_e^2)$

→ Estimated breeding values (ssEBV) for all animals in the pedigree

Heritability of resistance to paratuberculosis

$$h^2 = 0.14$$

h^2 very moderate

But $\sim h^2$ milk cell counts & $> h^2$ clinical mastitis

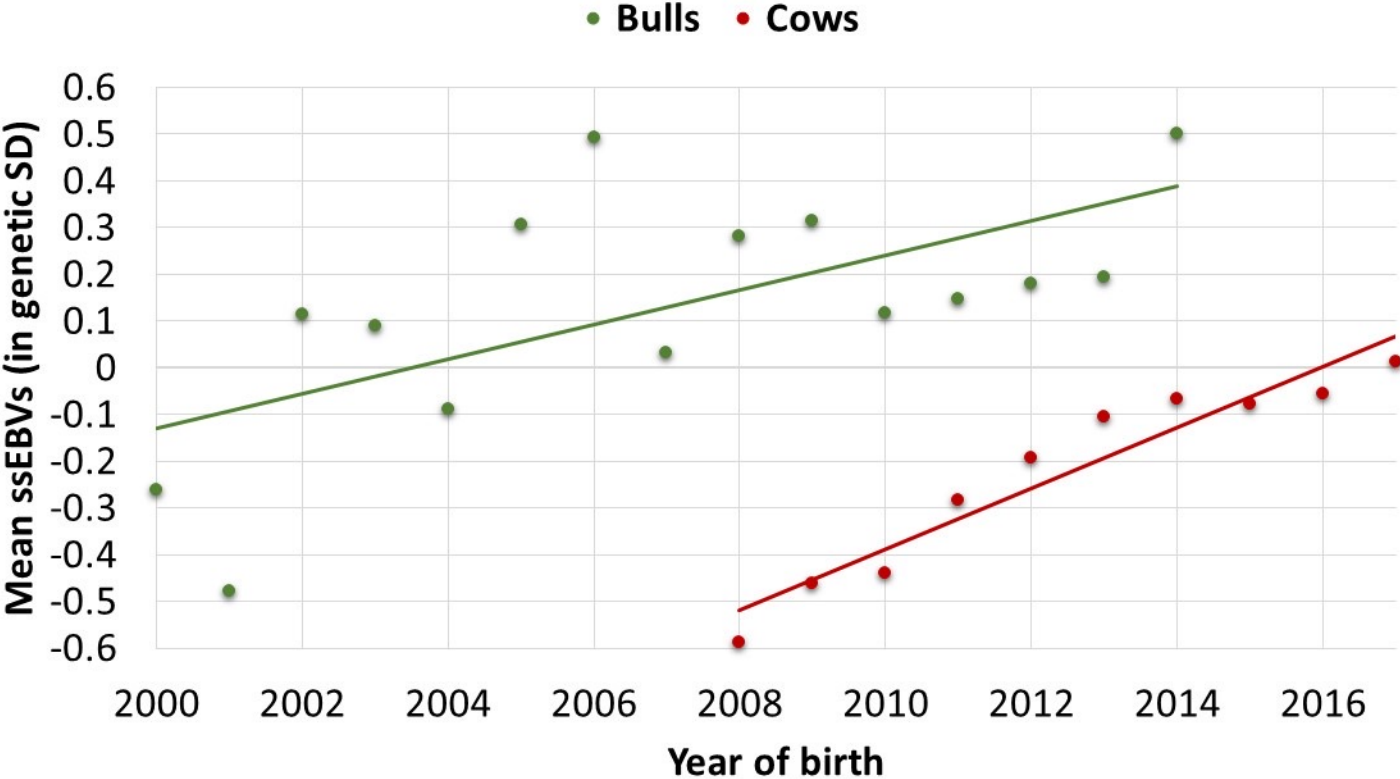
And consistent with values reported in the literature (0.03 – 0.27; Brito et al. 2018)

Realized genetic trends

ssEBVs means (in genetic SD) per birth year:

cows with statuses born between 2008 and 2017

bulls born between 2000 and 2014 with at least 10 daughters with statuses



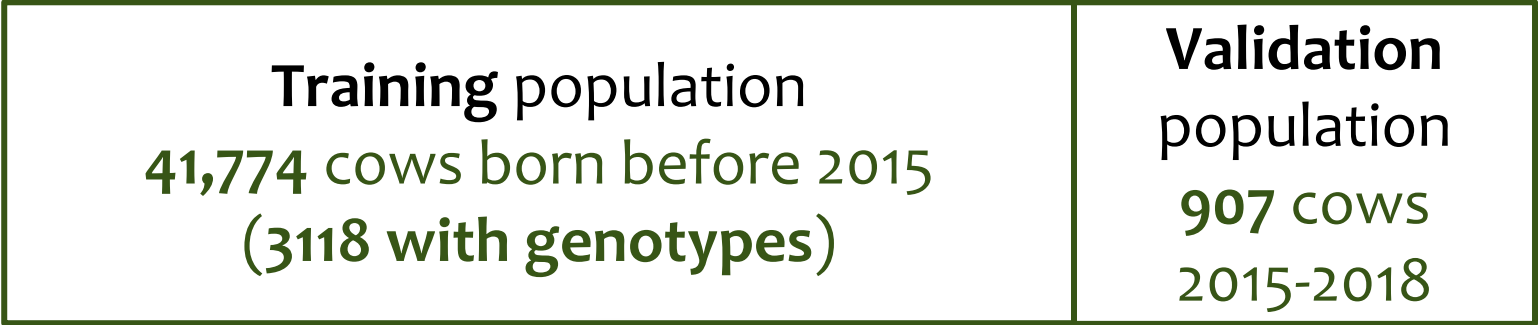
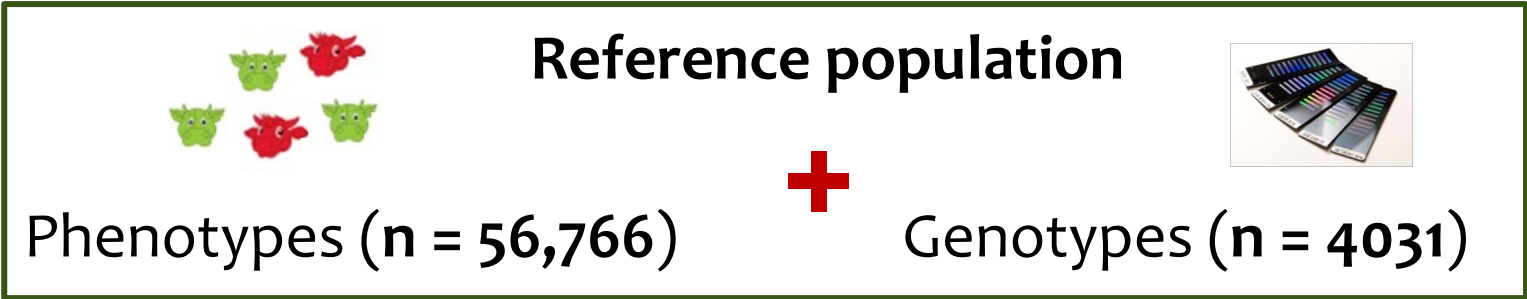
Moderate and favourable evolution of ssEBVs

On average:

+ 0.6 genetic SD between bulls born in 2000 and bulls born in 2014

Reliability of genomic predictions (GP)

Training / validation populations to estimate reliability of GP



Reliable GP,
estimated from a
reduced reference
population

$$\text{CD} = r(\text{GP, adjusted phenotype})^2 / h^2$$
$$= 0.28^2 / 0.14 = \mathbf{0.55}$$

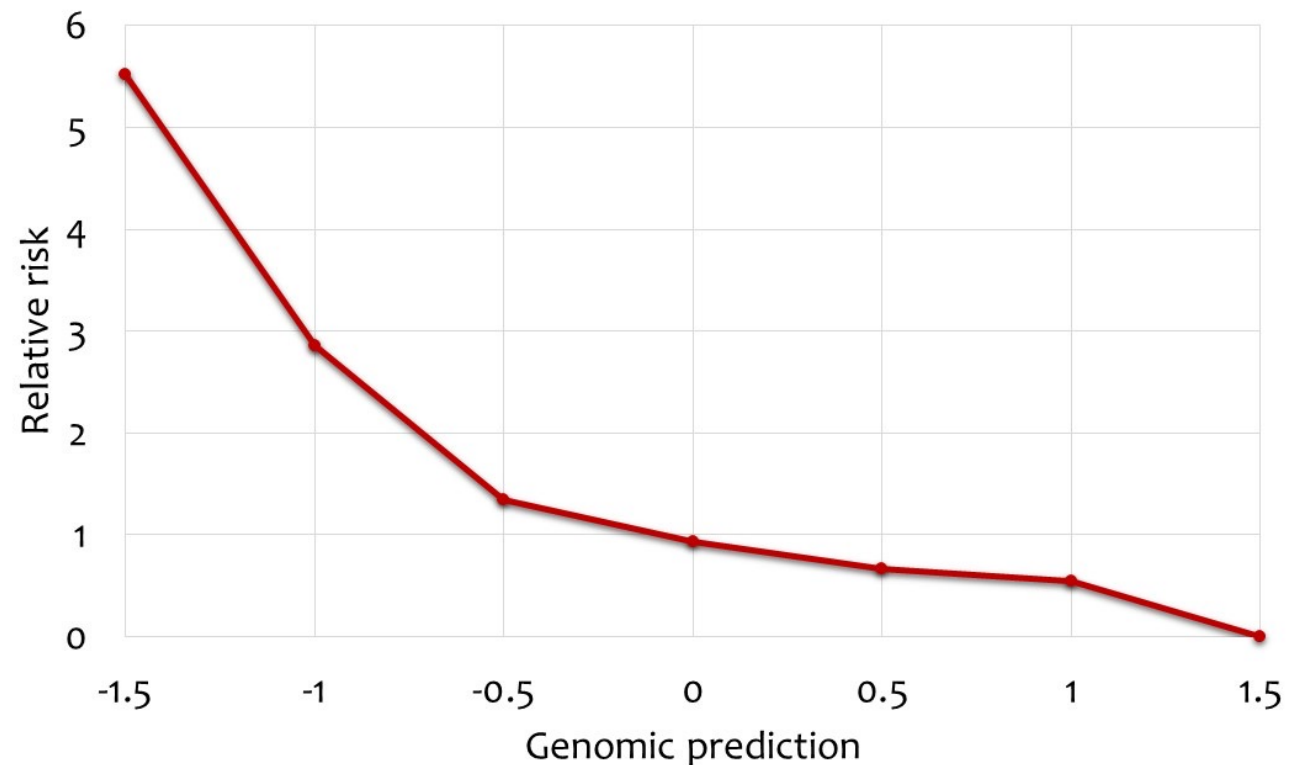
(correlation = 0.14 without a Single Step approach)

Risk factor

Relative risk factor estimated in the validation population
= relative risk of infection for a cow

0.5 point classes

Ratio of the proportion of infected animals in a given class to that in the central 0 class



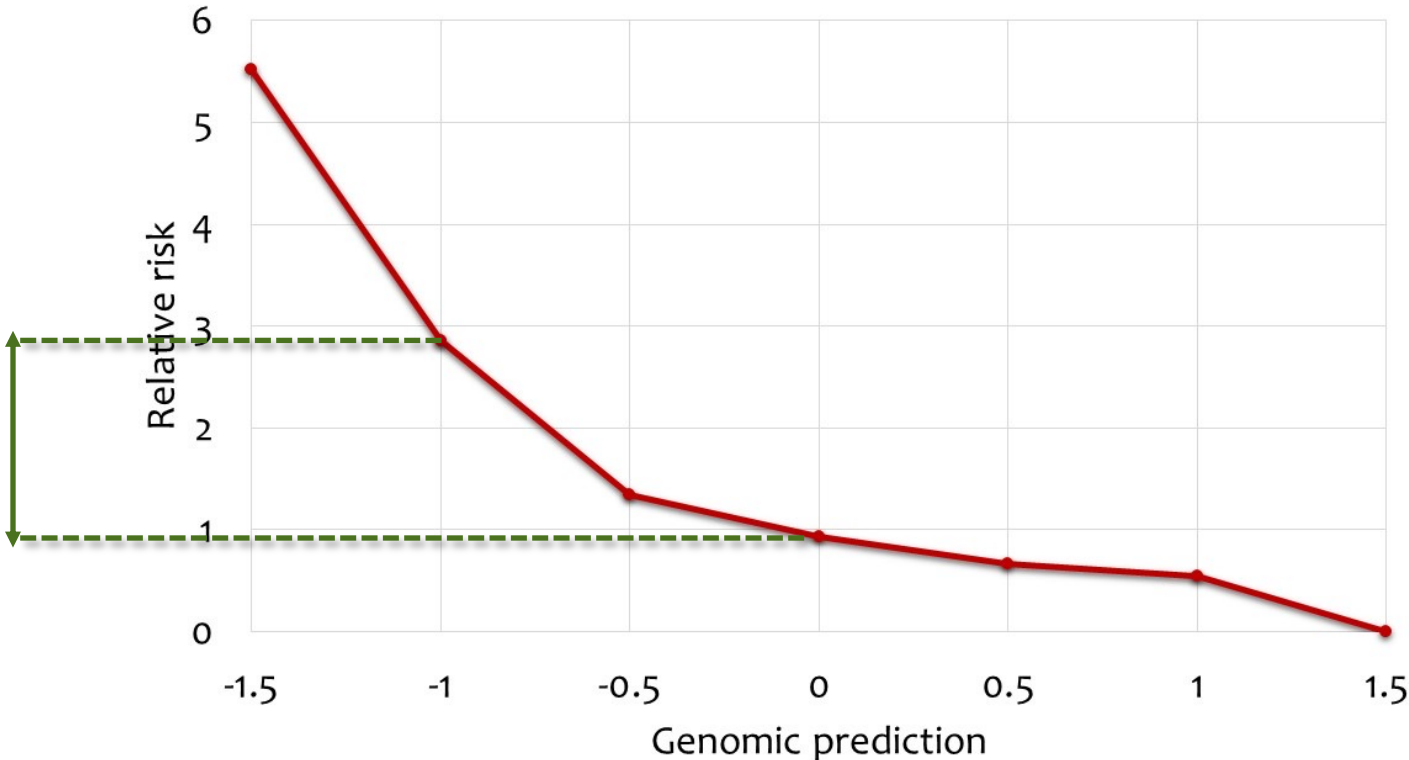
Risk factor

Relative risk factor estimated in the validation population
= relative risk of infection for a cow

0.5 point classes

Ratio of the proportion of infected animals in the class to that in the central 0 class

Risk **x3** for cows with GP of **-1**

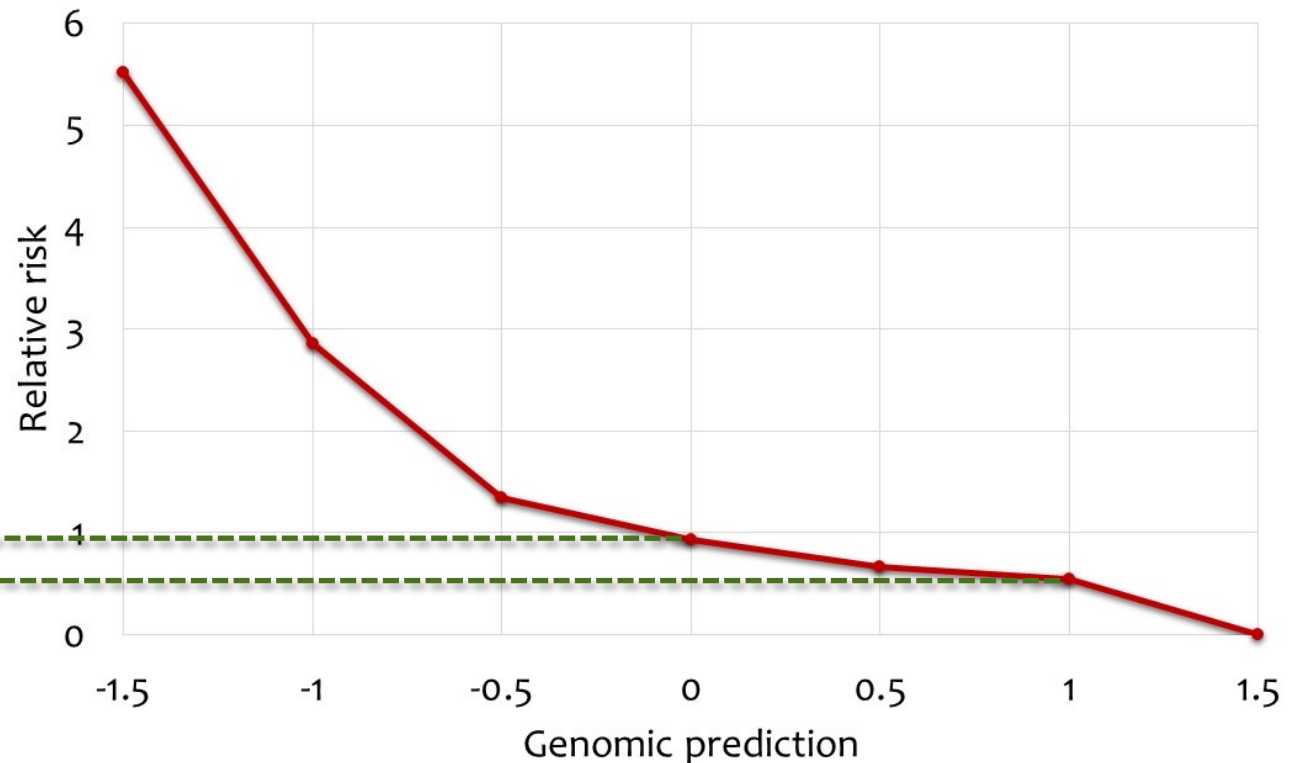


Risk factor

Relative risk factor estimated in the validation population
= relative risk of infection for a cow

0.5 point classes

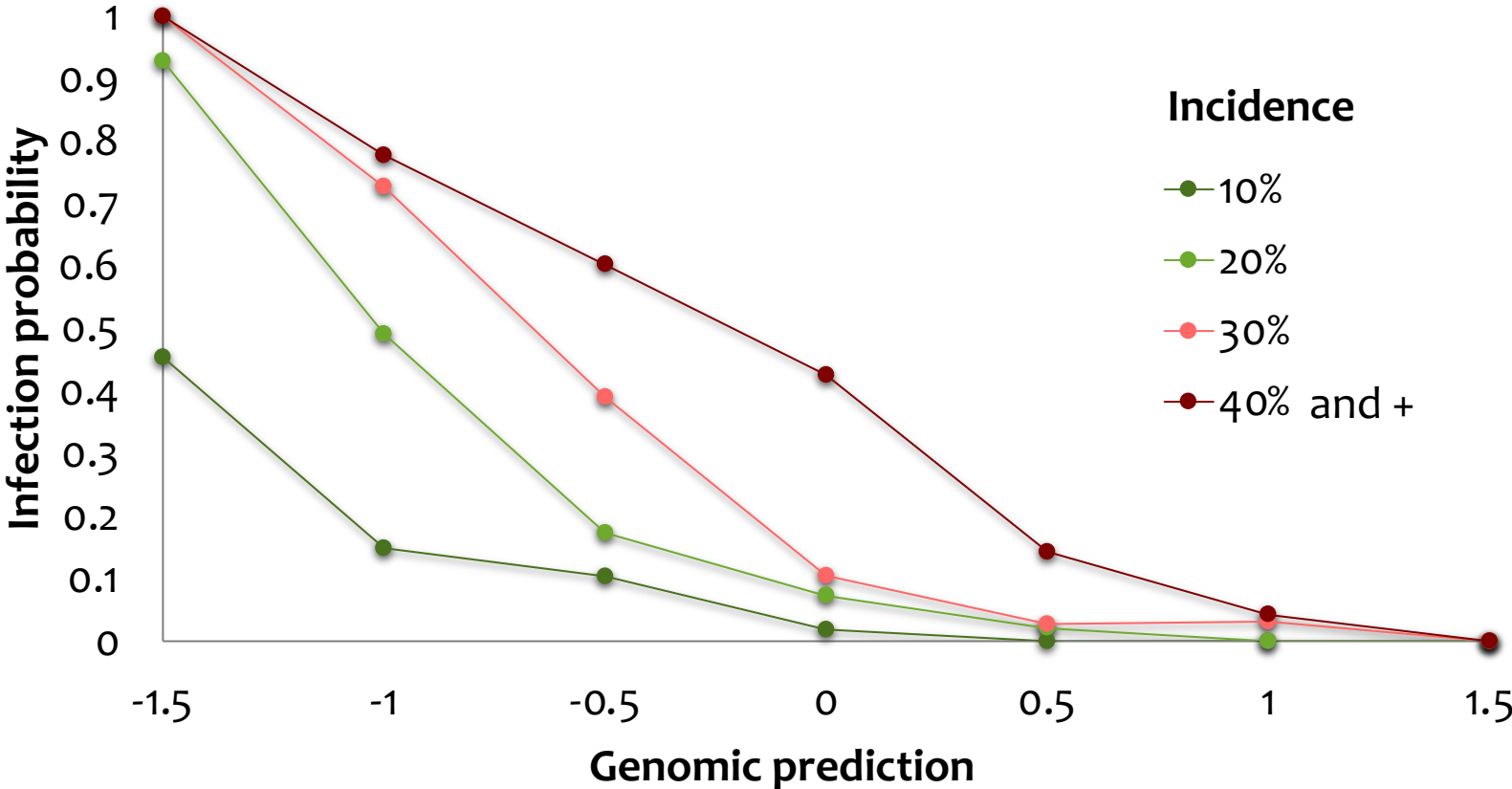
Ratio of the proportion of infected animals in the class to that in the central 0 class



Risk $\div 2$ for cows with GP of **+1**

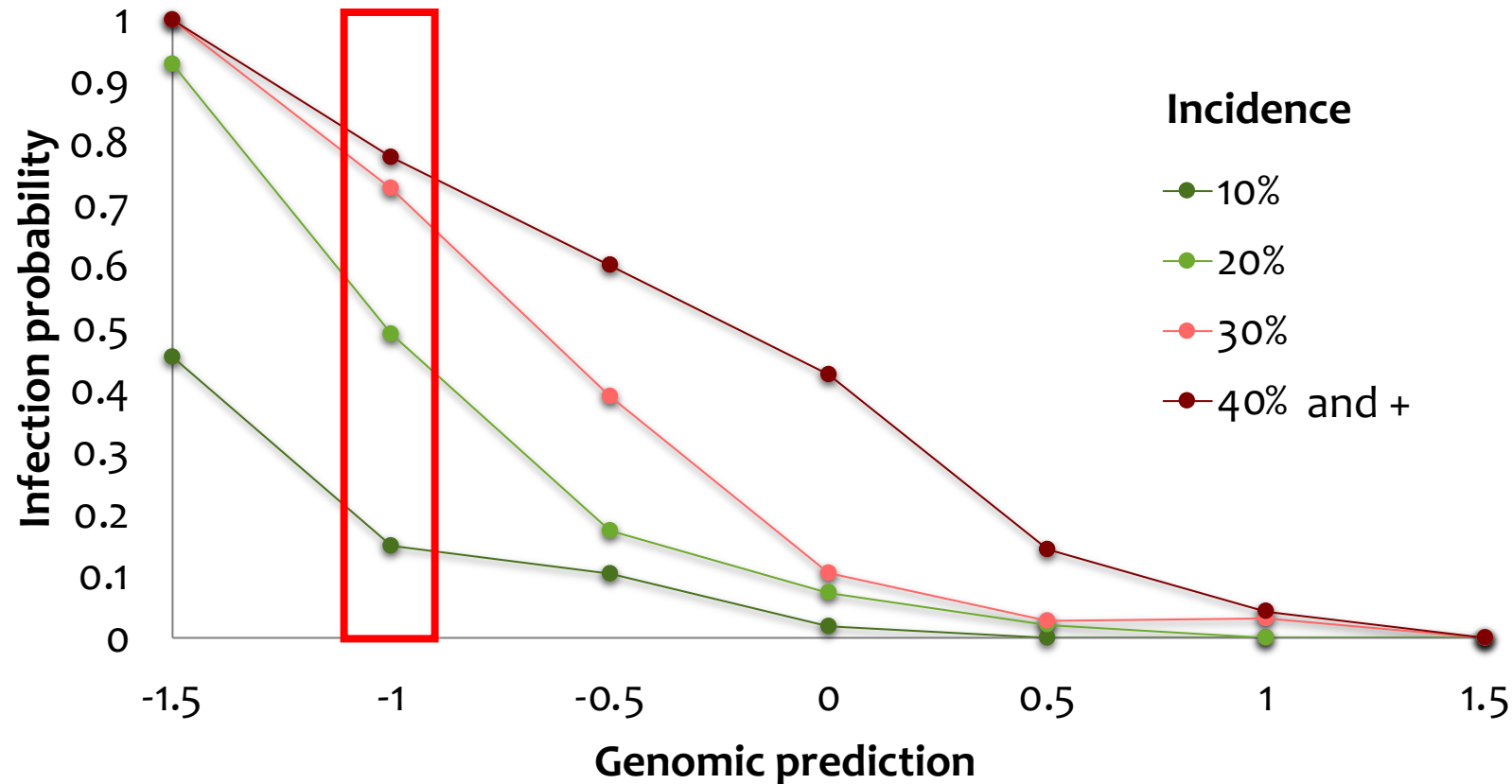
Risk factor

Relation between the probability of infection and GP depending on the incidence in the herd (training population)



Risk factor

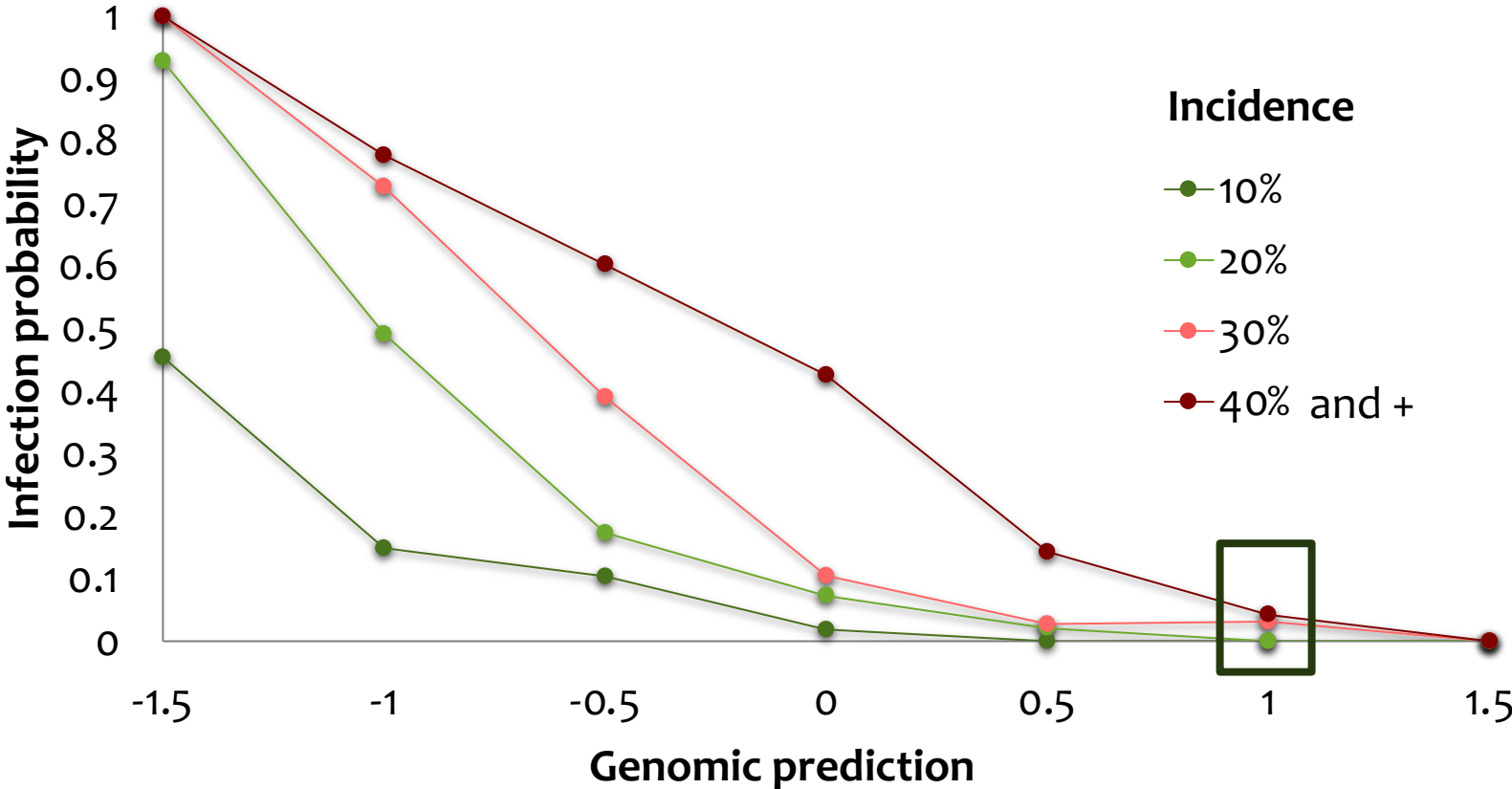
Relation between the probability of infection and GP depending on the incidence in the herd (training population)



Cows with GP = -1
The higher the incidence in the herd, the higher the infection probability

Risk factor

Relation between the probability of infection and GP depending on the incidence in the herd (training population)



The probability of infection of cows with GP = +1 is low regardless of the incidence in the herd

QTL detected via ssGWAS

From effects estimated in ssGBLUP
=> % genetic variance (%GV) explained
by windows of SNPs

$$\%GV_i = \frac{1}{n\sigma_\alpha^2} \hat{\mathbf{a}}_i' \hat{\mathbf{a}}_i$$

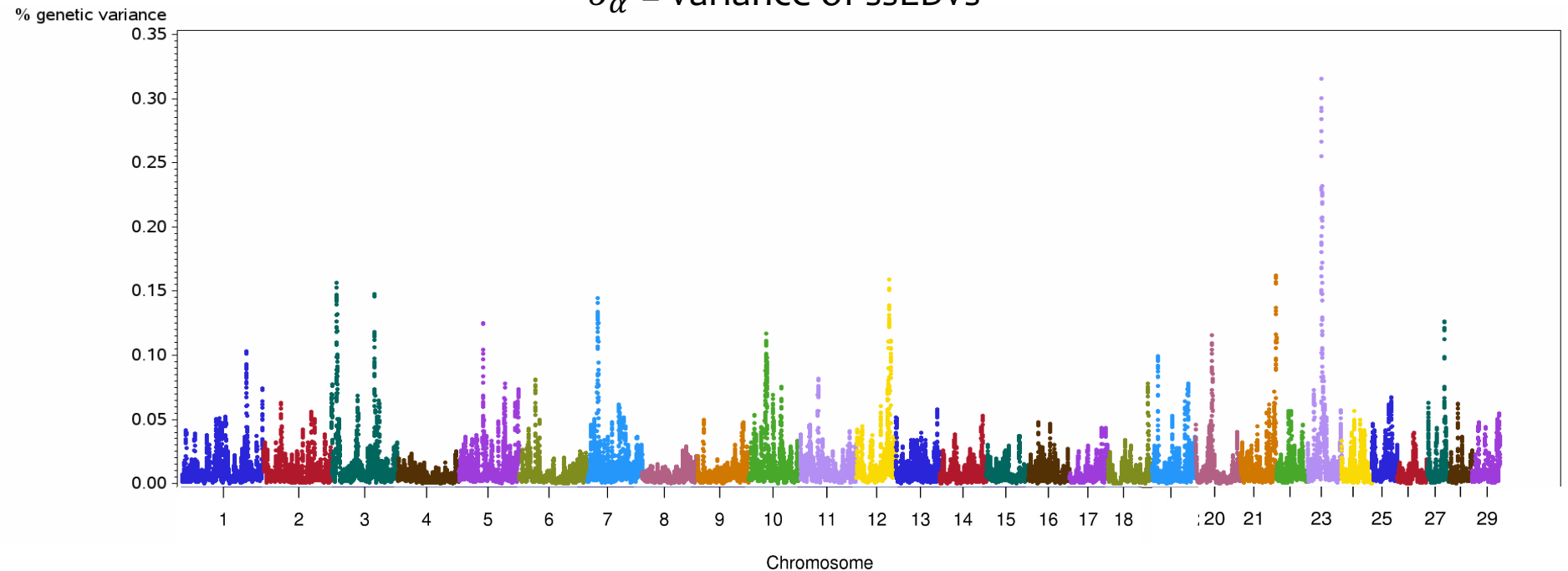
$\hat{\mathbf{a}}_i = \mathbf{M}_i \hat{\mathbf{s}}_i$ $\hat{\mathbf{a}}_i$ = vector of genomic values for the i^{th} region

\mathbf{M}_i = matrix of SNP content in region i

$\hat{\mathbf{s}}_i$ = vector of estimated effects of the SNPs in the region

σ_α^2 = variance of ssEBVs

Ex.
overlapping
windows of 25
SNPs



Confirmation of QTL detected on chromosomes 1, 3, 5, 12 and 23
+ detection of novel QTL on chromosomes 20, 21 et 27

Conclusions

Interest of a Single Step approach for the implementation of a genomic evaluation on resistance to paratuberculosis in Holstein

Sanchez et al. *Genetics Selection Evolution* (2022) 54:67
<https://doi.org/10.1186/s12711-022-00757-z>




RESEARCH ARTICLE

Open Access

New insights into the genetic resistance to paratuberculosis in Holstein cattle via single-step genomic evaluation



Marie-Pierre Sanchez^{1*} , Thierry Tribout¹, Sébastien Fritz^{1,2}, Raphaël Guatteo³, Christine Fourichon³, Laurent Schibler², Arnaud Delafosse⁴ and Didier Boichard¹

Conclusions

Genomic predictions weekly calculated since April 2022

Not included in the total merit index because their use depends on the herd status

Mainly used in infected herds:

- Culling of very sensitive females
- Higher control of sensitive cows
- Use of resistant bulls

Work in progress in **Normande** with an extension of the reference population (genotyping of cows with statuses)

Methodology applicable to other breeds



Thank you

PICSAR



PARADIGM

